IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of)
Laurent Di Constanzo et al.)
US patent application)Art Unit : 1615
N° 09/914,544
Filed: March 19, 2002) Examiner : OH.SIMON J

FOR : ORALLY DISPERSIBLE TABLET WITH LOW FRIABILITY AND METHOD FOR PRODUCING SAME

DECLARATION UNDER RULE 132

To Honorable Commissioner of Patents and Trademarks
Washington, D.C.
Sir :

I, Edouard GENDROT, 24, rue de Dreux 28500 GARNAY, France, do solemnly declare :

THAT I am a named inventor of the present patent application n° 09/914,544 and that I am fully familiar therewith ;

THAT I have read and understood the Office Action of September 14, 2004 in connection with the present patent application ;

THAT I have carefully read Liu et al. (US 6,465,009) and clearly understood said patent ;

THAT, tablets according to Liu et al. are different from tablets according to the invention since they are manufactured thanks to a process which is not a direct compression of a mixture of powders ;

THAT, the process according to Liu et al in which successive steps of hydration and drying of the mixture of constituents before the compression are carried out, leads to tablets presenting an internal microscopic structure different from the structure of the tablets according to the invention ;

THAT, the disintegration of the tablets according to Liu et al. is carried out by the fact that one component is a water soluble binding agent (PVP) which dissolves when the tablet is put in presence of water ;

THAT, tablets according to the invention comprise a disintegrant, which is not water soluble, e.g. crospovidone (cross-linked PVP), and when the tablet is in the presence of water, said disintegrant make the tablet exploded, with no solubilisation ;

THAT, consequently, Liu et al. does not describe, nor suggest tablets according to the invention.

I, the undersigned, declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001, of Title 18, of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: February 10 of 2005

Edouard GENDROT

Kollido

Polyvinylpyrrolidone for the pharmaceutical industry

ENCLOSURE A

Kollidon®

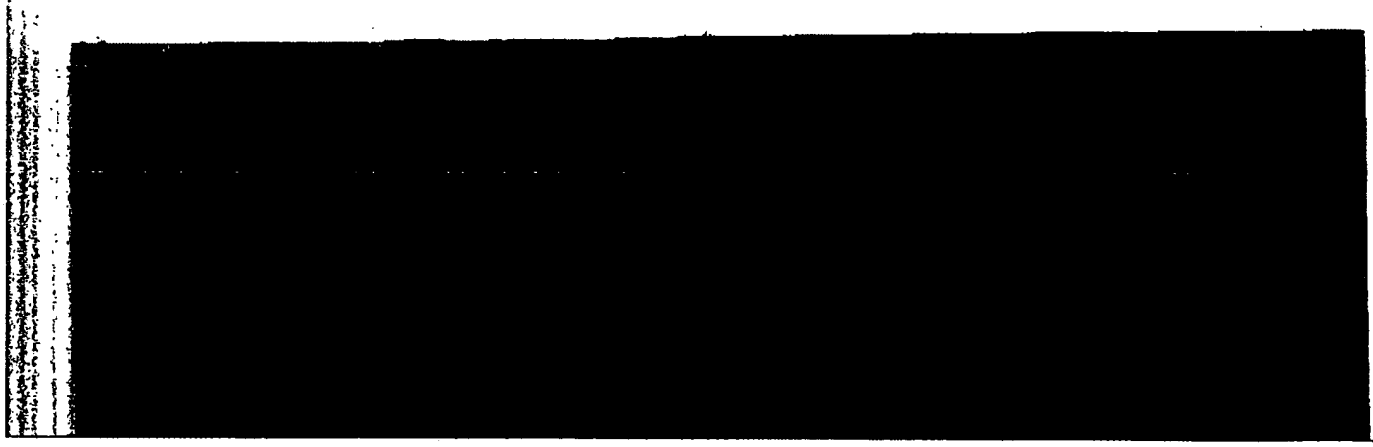
Polyvinylpyrrolidone for the pharmaceutical industry

BASF Aktiengesellschaft
Fundname
D-67056 Ludwigshafen

BASF

May 1996
(3nd edition)

Contents



1 General notes on synthesis and applications

1.1 Soluble polyvinylpyrrolidone (soluble Kollidon grades)

Modern acetylene chemistry is based on the work of Reppe at BASF. One of the many products of this work is N-vinylpyrrolidone (Fig. 1).

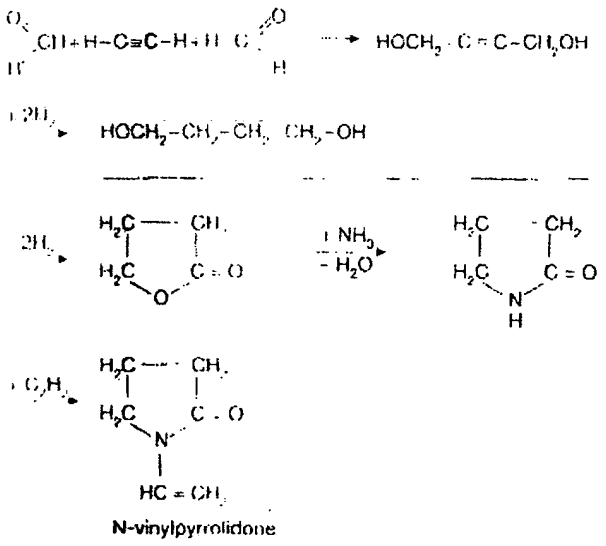


Fig. 1 Reppe synthesis of N-vinylpyrrolidone (C_6H_9NO, M_r 111.1)

The first polymerization product of N-vinylpyrrolidone was soluble polyvinylpyrrolidone, which was patented in 1939. Fig. 2 shows one of the mechanisms of polymerization: free radical polymerization in water using hydrogen peroxide as initiator [1, 141].

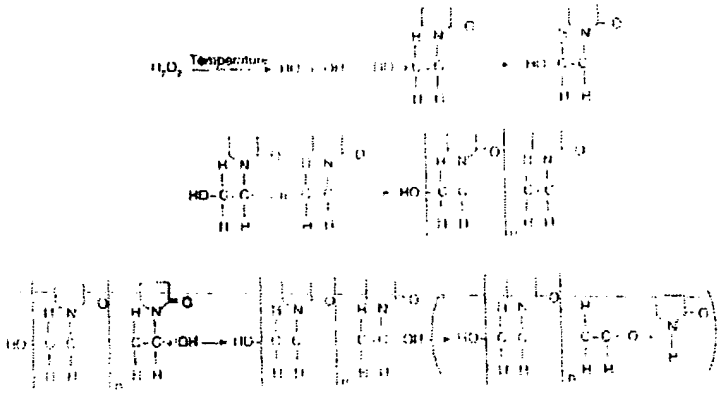


Fig. 2 The reaction mechanism for the radical polymerization of N-vinylpyrrolidone in water

The mechanism for terminating the polymerization reaction makes it possible to produce soluble polyvinylpyrrolidone of almost any molecular weight.

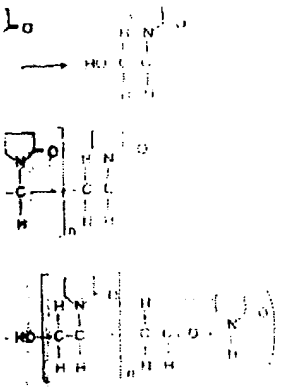
Apart from the method of production in water shown in Fig. 2, it is also possible to conduct the polymerization in an organic solvent, e.g. isopropanol. This technology is used today in the production of low-molecular polyvinylpyrrolidone for injection solutions.

The low and medium-molecular weight grades of soluble polyvinylpyrrolidone are spray-dried to produce the pharmaceutical grade Kollidon powders, while the high-molecular weight grades are roller-dried.

Soluble polyvinylpyrrolidone was first used during World War II as a blood-plasma substitute. Although it has excellent properties for this purpose, it has no longer been used for a number of decades. The organism does not metabolize the polymer, with the result that after parenteral administration, small quantities of high-molecular components may remain within the body. This problem does not exist with oral administration.

Today, soluble polyvinylpyrrolidone (e.g. Kollidon) is one of the most versatile and widely used pharmaceutical auxiliaries (see Chapter 2.4 "Soluble Kollidon grades").

It is also used in the production of one of the most important topical disinfectants, PVP-Iodine.



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1.2 Insoluble polyvinylpyrrolidone (e.g. Kollidon CL)

Insoluble polyvinylpyrrolidone is obtained by popcorn polymerization of N-vinylpyrrolidone [2], which yields a crosslinked polymer [4 – 6]. The process is illustrated in Fig. 3 and uses either an alkali hydroxide at temperatures over 100 °C, which yields some bifunctional monomer, or a small percentage of bifunctional monomer in water to initiate crosslinking of the polymer.

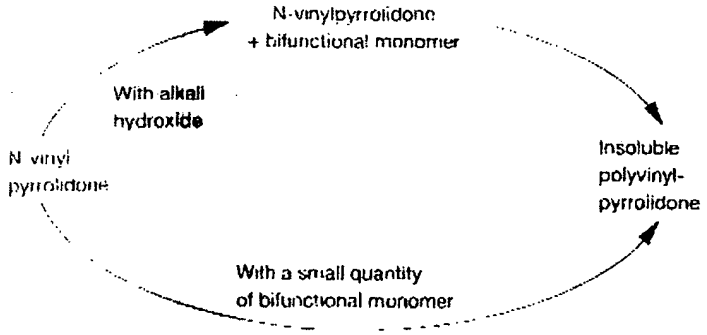

Fig. 3 Production processes for insoluble N-vinylpyrrolidone popcorn polymers

A comparison of the infrared spectra of the insoluble popcorn polymer obtained as shown in Fig. 3 and that of soluble polyvinylpyrrolidone shows practically no difference, while the infrared spectrum of chemically crosslinked insoluble polyvinylpyrrolidone polymer prepared in the laboratory is quite different, which indicates that the crosslinking in the popcorn polymer is essentially of a physical nature.

Insoluble polyvinylpyrrolidone finds extensive applications in the pharmaceutical and beverage industries as a swelling popcorn polymer with selective adsorptive properties. Its disintegration effect in tablets, its ability to hydrophilize insoluble active ingredients and to adsorb and form complexes are the main properties that make it useful as a pharmaceutical auxiliary. Today, Kollidon CL is regarded as one of the "superdisintegrants" for tablets.

Further, micronized insoluble polyvinylpyrrolidone is of considerable significance as an active substance against diarrhoea in certain parts of the world.

3.4 Applications of the insoluble Kollidon grades and Crospovidone M

3.4.1 General application properties

The insoluble grades of Kollidon and Crospovidone M possess a series of properties that are used in the manufacture of different pharmaceutical products.

Table 10: Functions and properties of Kollidon CL, Kollidon CL-M and Crospovidone M in pharmaceuticals

Acceleration of tablet disintegration and therefore also of dissolution and bioavailability of the active substances as a result of predictable swelling (disintegration effect)

Improvement of dissolution and bioavailability of drugs by complex formation

Selective adsorption of polyphenols by complex formation

Stabilization of suspensions by Kollidon CL-M as a hydrophilic polymer

Stabilization of vitamins

Adsorption of endotoxins by complexation

Adsorption of water

Taste masking of acetaminophen

The most important property of Kollidon CL as an auxiliary is its *disintegration effect*, which can be used in tablets, granules and hard gelatin capsules.

Its ability to form *complexes* is useful in solid and liquid dosage forms.

The improvement brought about by Kollidon CL and Kollidon CL-M in the dissolution of drugs is particularly useful for tablets and granules.

The use of Crospovidone M as an active substance against diarrhoea depends, on its ability to form complexes, as does the use of crospovidone ("PVPP") in removing polyphenols from wine, beer and plant extracts. The ability of Kollidon CL-M to *stabilize suspensions* finds its most important application in antibiotics, antacids and vitamin preparations.

The hygroscopicity of Kollidon CL and Kollidon CL-M (see Section 3.2.3.2) can be used to *absorb water* in preparations that contain moisture-sensitive drugs, to improve their stability. It almost certainly also contributes to the efficacy of Crospovidone M as an active substance in the treatment of diarrhoea.

(Cont.)

2.4 Applications of the soluble Kollidon grades

2.4.1 General properties

The soluble grades of Kollidon possess a number of very useful properties for which they are widely used in pharmaceuticals.

Because of these properties, the products can perform different functions in different dosage forms.

Table 1: General properties of the soluble Kollidon grades in pharmaceuticals

Solubility in all conventional solvents
Adhesive and binding power
Film formation
Affinity to hydrophilic and hydrophobic surfaces
Ability to form complexes
Availability in different average molecular weights
Thickening properties

Their excellent *solubility* in water and in other solvents used in pharmaceutical production (Section 2.2.2) is an advantage in almost all dosage forms, e.g. in wet granulation in tablet production, in oral solutions, syrups and elixirs, in injectables and topical solutions and in film coatings on tablets.

Their *adhesive and binding power* is particularly important in tableting (wet granulation, dry granulation, direct compression). This property is also useful in film coatings and adhesive gels.

Their *film-forming properties* are used in the film coating of tablets, in transdermal systems and in medicinal sprays.

Their *affinity to hydrophilic and hydrophobic surfaces* is particularly useful in the hydrophilization of a wide range of substances, ranging from hydrophobic tablet cores - to permit sugar or film coating, to medical plastics.

Their ability to form *complexes* with such a large number of substances is a special feature of the Kollidon grades (Section 2.2.4). The complexes formed are almost always soluble and are stable only in an acid medium. This property can be used to increase the solubility of drugs in liquid dosage forms, as in the case of PVP iodine. In solid dosage forms, the ability to form complexes is used to increase bioavailability. A reduction in the local toxicity of certain drugs can also be achieved by complexation with Kollidon.

A special use for the complexation properties of Kollidon lies in the stabilization of proteins and enzymes in diagnostics.

Their *thickening properties* (Section 2.2.3) are used in oral and topical liquid dosage forms, e.g. syrups and suspensions.

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Table 1.1: Some applications of polymers in the pharmaceutical industry

Function	Pharmaceutical form
Binders	Tablets, capsules, granules
Disintegrant, enhancer	Tablets, capsules, granules, pellets, suppositories, transdermal systems
Film formers	Ophthalmic solutions, tablet coats, medical plastics
Solubilizers	Oral, parenteral and topical solutions
Lubricant/binder	Oral solutions, chewing tablets
Crystallization agent	Injectables, oral lyophilisates
Suspension stabilizer	Suspensions, instant granules, dry syrups
Cryoprotectant	Medical plastics, sustained release forms, suspensions
Adhesive	Transdermal systems, adhesive gels
Stabilizer	Enzymes in diagnostics, different forms
Iodine solubilizer	Povidone iodine
Toxicity reduction	Injectables, oral preparations etc.

They are available in grades of *different average molecular weight* (Section 2.2.6), so that above properties named all depend on the molecular weight, to a greater or lesser extent.

With increasing molecular weight, the dissolution rate of the soluble Kollidon grades decreases, while the adhesive power, the viscosity and often also the ability to form complexes increase. The rate of elimination from the organism after parenteral administration decreases with increasing molecular weight.

The dependence of the properties on the molecular weight makes it possible to provide the optimum grade for each dosage form or formulation and to achieve the optimum effect.